A STUDY OF THE EFFECTS OF ACUTALYN R/ ON THE EXPERIMENTALLY INDUCED UREMIA IN CANINES

by

MAHARAJAPURAM SUBRAMANIA GANAPATHY

B. V. Sc., Madras University, 1940

A THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Surgery and Medicine

KANSAS STATE UNIVERSITY
OF AGRICULTURE AND APPLIED SCIENCE

1960

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INTRODUCTION

Uremia is a clinical syndrome wherein there is retention of a variety of waste products of metabolism in the circulating blood, thereby altering its chemical composition. These products are normally eliminated in the urine.

The principal substances retained are urea, uric acid, creatine, creatinine, glutothione and many others of unknown nature, all of which are referred to as Non-protein Nitrogen (N.P.N.) of the blood. Of these urea constitutes 45 percent of the total N.P.N. (25). Within recent years there has been a significant shift in emphasis from the retention of protein waste products in uremia to more important biochemical derangements, such as disturbances in water balance, acid-base equilibrium and changes in the electrolyte structure (40). Whatever the genesis of the uremic episode, the retention of the nitrogenous waste products serves as the spark that sets up a series of chain reactions which may be attributed to the clinico-pathologic manifestations of uremia.

Incidence of Uremia in Dogs

The kidney, through its remarkable functions of filtration, resorption and excretion, occupies a key position in maintaining the normal equilibrium of the various chemical substances which bathe the cells of the body in health. In deranged functions of this organ, this equilibrium is upset and there occurs in the blood an increase of those constituents normally eliminated in the urine. Hence uremia is usually associated with acute or chronic renal insufficiency.

Like many other vital organs such as the heart, brain, lung and liver the kidney is endowed with an enormous reserve of functional tissue. The kidney consists of a collection of 1-2 million nephrons, each comprised of a glomerulus and a tubule. Approximately one-fourth of these nephrons should be functional for normal renal health. As nephrons are destroyed each remaining functional unit must take on more of the renal work load (31).

Pathologists agree that the majority of dogs have kidney lesions by the time they reach middle age and it has been estimated that 50 percent of old dogs die from kidney disease (51). Evidence of interstitial nephritis may be found in 55 percent of routine autopsy cases and in 80 percent of dogs eight years of age or older at the time of necropsy (6). According to Bloom (6), interstitial nephritis is responsible for about 89 percent of all cases of uremia. There is no special breed incidence but the disease terminates in uremia in approximately eight males to one female. Most clinical cases of chronic interstitial nephritis follow leptospiral infection (32). The serological survey by Meyer and co-workers (39) has established that Leptospira canicola is the primary cause of leptospirosis in dogs in this country. It is in the chronic form of this disease, which is difficult to diagnose that the finding of an elevated Blood Urea Nitrogen (B.U.N.) is of diagnostic importance (41). Dickson (17) reports that uremia is most frequently observed in dogs between the ages of six to nine years. Animals with renal diseases which have an excessively high protein intake, especially if a poor quality protein makes up a large percentage of feed, will be prone to develop uremia (31).

Retention of urinary constituents in the blood may also occur in normally functioning kidneys, due to obstruction to the free flow of urine resulting

from urinary calculi or an enlarged prostate pressing on the urethra, intestinal obstruction, acute pancreatitis, disturbance of water and electrolyte balance occurring in dehydration or starvation and in rupture of the bladder. Causes of rupture of the bladder are various types of trauma such as automobile injuries, crush injuries, jumping or falling from heights and blows over the abdomen, particularly when the organ is distended with urine (7). Other causes of vesical rupture detailed by Bloom include the possible rupture of a distended bladder in the male dog during sexual act and in the female in prolonged and difficult labor. Perforations of the bladder may occur in fractures of the pelvis, careless catheterization, in bullet or knife wounds and accidental incision during abdominal surgery. In such an event, the urine escapes into the abdominal cavity. The urinary waste products are absorbed through the vast expanse of peritoneum resulting in uremia. In the case of contaminated urine, one should expect septic peritonitis in addition to the uremic syndrome.

Pathogenesis of Uremia

The origin of the uremic syndrome is not clear. The idea that the simple concentration of urea in the blood is responsible, has been abandoned. However nitrogen retention is still regarded as the initiating factor of uremia. Other factors are disturbances of the water and electrolyte metabolism and in the equilibrium of acid-base balance resulting in serious abnormalities of the chemical composition of body fluids (4). There is hemoconcentration and a strong tendency towards acidosis. The depletion of chloride from the blood is brought about by incessant vomition. Hypocalcemia

produces parathyroid hyperplasia resulting in metastatic calcification and osteodystrophic fibrosa. The cause of death in uremia has been attributed to cardiac arrest by potassium poisoning.

Origin and Fate of Urea in Health

It has been demonstrated that the liver is the principal seat of urea formation. The mechanism of urea formation by the liver is not clear; however it is the current opinion that urea is formed in the liver from the amino acids, arginine and glutamine by enzymatic action.

Urea thus formed finds its way into the general circulation and is excreted by the kidney. It is completely filtered through the glomerulus. Forty-sixty percent of the filtered urea diffuses out of the tubules and back into the capillaries (11). The tubular resorption depends on the rate of flow of urine and the plasma concentration of this substance. The normal blood urea range in dogs is from 20-40 mgm percent (13). In impaired renal function, obstruction to the urinary flow and in cases of vesical rupture and consequent resorption of urinary constituents there is a resultant quantitative variation in the concentration of blood urea. It has also been shown that the amount of urea formed in the body in full grown mammals is approximately proportional to the nitrogen intake (11).

Blood Urea Nitrogen in Uremia

All investigators agree that the symptoms of uremia are associated with a high degree of nitrogen retention. The estimation of urea nitrogen is preferred to the estimation of non protein nitrogen because its determination is relatively simple and it has greater variation in disease. Signs

of renal insufficiency ordinarily appear when the B.U.N. approaches 50 mgm percent. In the terminal stages of uremia the B.U.N. may be as much as 300 mgm percent. Crandall's survey of blood urea levels in hospitalized dogs showed a range of 40-260 mgm percent. Comparative studies have shown that if the blood urea is 40 mgm the blood urea nitrogen will be 18 mgm. Cases that showed a level of 260 mgm percent and over died. If correlated with the clinical picture and other laboratory procedures, B.U.N. is probably one of the most useful tests available to the small animal practitioner (5).

Symptoms of Uremia

The classical symptoms of uremia are somnolence, progressive emaciation, anorexia, polydipsia, nausea, vomition and other gastro-intestinal disturbances, congested mucous membrane, normal to subnormal temperature, fetid mouth odor associated with necrotic stomatitis and occasionally hypoplastic anemia.

Treatment of Uremia

Although the treatment of uremia is generally unrewarding, the objectives in therapy should be to prevent further kidney damage, to make the work load of the residual functional nephrons as light as possible, to prevent the build-up of non-protein nitrogenous constituents of the blood by judicious dietary regimen, to remove any possible obstruction to the free urinary flow and in case of vesical rupture, to repair the damage to the bladder wall by surgery with the least possible delay.

Parenteral feeding may be necessary because of the hyper-irritability of the gastric mucosa. The electrolyte balance should be restored by

appropriate fluid therapy. Peritoneal lavage has been found to be of benefit in acute uremia in leptrospirosis (30). When a lavage fluid approximating the electrolyte composition of the tissue fluid is injected into the peritoneal cavity, the peritoneum acts as a dialysing membrane. Urea, other waste products of metabolism and all electrolytes not present in the lavage fluid escape into the peritoneal fluid by diffusion. The lavage fluid is withdrawn at the end of two hours and the procedure repeated two or three times a day. Dogs have been kept alive as long as 111 days by this intermittent peritoneal lavage which serves as a substitute for the excretory but not the metabolic functions of the kidney. Desoxycorticosterone acetate (D.C.A.) has been used to hasten the elimination of urea, endogenous creatinine and potassium (17). Antibiotics have their place in the treatment of uremia, particularly in leptospiral infection. Oral administration of aluminum hydroxide will prevent additional absorption of phosphate from the digestive tract by forming insoluble aluminum phosphate which is excreted by the intestinal tract.

Acutalyn R/

As early as 1947, experimental work of Ershoff (18) indicated the existence of a factor in whole liver which provided significant protection in rats against the toxicity of thyroid. This liver fraction has been shown in subsequent studies to counteract the deleterious effects of toxic doses of such drugs as atabrine, alpha estradiol, dinitrophenol, acetyl salicylic acid, thiourocil and cortisone acetate. Rats exposed to unusual physiological stress as swimming at cold temperature or exposure to multiple doses of x-irradiation stood the physical challenge well under the protective influence of this liver fraction. This 'antitoxic factor' has been shown by

Erschoff to be distinct from any of the known vitamins. Harper and Henry (14) in late 1955 reported encouraging clinical response in arthritis in man after the administration of a crude water soluble hepatic fraction. Acutalyn was first refined and standardized by the Enzyme Products Laboratories in 1956 from a crude liver protein fraction. Experimental studies have shown the beneficial effect of Acutalyn R/ in canine polyarthritis, equine lameness, blood dyscrasias and other metabolic disorders (14). With adequate supportive therapy in the form of B-vitamins and parenteral fluids, Mosier (43) found dramatic response from Acutalyn R/ in cases of uremia in dogs. There was a reduction of elevated B.U.N. to normal levels besides the evidence of clinical improvement. Those cases which did not respond to Acutalyn R/ showed on necropsy irreversible tissue damage in the kidney to the extent that parenchymatous regeneration would be improbable.

In this study an attempt was made to induce uremia by artificial rupture of the bladder and allowing the urinary waste products to be reabsorbed through the peritoneal lining. The effect of repair of the bladder defect by surgery at the end of 24 hours on the symptomatology, course, recovery rate and the pattern of B.U.N. was studied. Acutalyn R/ was administered to those animals in whom uremia was experimentally induced and also to those who had the bladder defect repaired and the results evaluated.

REVIEW OF LITERATURE

In recent years an impressive volume of research has centered around the etiology of uremia, its relation to the functional activity of the kidneys, the pathogenesis of the condition and the value of B.U.N. in the diagnosis and prognosis of this syndrome.

As to the etiology of uremia, at one time or another almost every known urinary constituent has been incriminated as the toxic substance which causes the uremic symptoms. To date no investigator has been able to pin point any single substance as the 'uremic toxin'. It may be that such a unitary explanation of uremia does not exist. All available evidence indicates that uremia is the complex result of a multiplicity of mechanisms set in motion by impaired renal function (19). Grace et al. (21) agree with Cantarow and Trumper that the symptom-complex of uremia is fundamentally dependent upon the marked interference with the functional activity of the kidneys. Kolmer (34) stresses the retention in the blood of urinary waste products in uremia. Bloom (9) observes that in both health and disease the degree of nitrogen retention depends on the functional state of the kidneys, volume of urine and the capacity of the kidneys to concentrate urine. Fishberg (19) is emphatic regarding the importance of N.P.N. in the blood in uremia, and states that 'no group of symptoms is to be considered as uremic in nature unless it occurs in the presence of abnormally high N.P.N. in the blood'. Among the 186 dogs treated for chronic interstitial nephritis at the Angell Memorial Hospital during 1943, Schnelle (49) found a high degree of nitrogen retention in these patients. According to Mosier (41) leptospirosis, in the chronic form, runs an insidious course extending from one to one and a half years with death occurring from terminal uremia. Grimm (22) has reported a case of uremia associated with renal calculi and nephritis in a ten year old female Boxer. The occurrence of vesical injuries is frequently reported in man and animals, especially since the advent of automobile. Herman (26) states that in man rupture of the bladder is the common major vesical injury encountered in practice. In the dog and cat

it is of frequent occurrence and is of clinical and pathologic significance (7). One would expect a high B.U.N. in these patients with rupture of the urinary bladder, yet no data is available as to the incidence of uremia in natural or induced rupture of this organ.

Wide variations of B.U.N. values in normal dogs have been reported by different workers. Table 1 gives the source and the values of B.U.N.

Table 1. Blood urea nitrogen in normal dogs.

Serial No.	No. of dogs examined	Maximum B.U.N. Mgm %	Minimum B.U.N. Mgm %	Average Mgm %	Source
1	20	22.60	10.00	15.50	Allison et al.
2	28	—	—	11.04	Foss & Routt
3	6	—	—	12.90	Morgulus and Edwards
4	200	—	—	11.70	Hadden & Orr
5	4	20	11	14.20	Coffin & Gabasso
6	—	20	8	—	Bollman & Adler
7	—	40*	20*	—	Crandall

*Blood Urea percent.

Most investigators of this syndrome are agreed on the diagnostic importance and prognostic significance of B.U.N. Theobald (53) reports the determination of B.U.N. is not only useful in diagnosis but is of value in prognosis. The condition of a dog with urine of low specific gravity and a high blood urea portends a grave prognosis. The general resistance is lowered in dogs with very high B.U.N. values. The importance of the urea concentration in the blood lies in its value as an indicator of kidney function. Elevation

of B.U.N. signifies inadequate kidney function. It has been found by experimental study that the amount of urea found in cases of naturally occurring uremia, when injected into experimental dogs, did not produce the uremic symptoms. Apparently there are toxic substances of unknown nature which are retained in the blood in rough proportion to the urea level. It is for this reason that a high N.P.N. or B.U.N. level is a matter of grave concern to the clinician (2). Huff and Pearson (28) found in addition to other clinical laboratory procedures, the B.U.N. test was most helpful in determining what treatment, if any, was indicated. However they caution that the B.U.N. must be considered with other clinical signs before making a prognosis. Using Lamotte's technique of blood urea determinations, Thomas (54) found a B.U.N. range from 250-400 mgm percent in animals with leptospirosis or nephritis. Schnelle (49) found a high blood urea value in most cases of leptospirosis and in chronic interstitial nephritis in dogs brought to the Angell Memorial Hospital for treatment. The highest level of B.U.N. in dogs observed by Mosier (41) at the Kansas State Veterinary Clinic has been 480 mgm percent. The highest value of B.U.N. noted by Phillips (46) has been 280 mgm percent. Phillips agrees that most animals in these higher ranges are terminal and beyond restoration. Crandall (13) is convinced, after his survey of blood urea levels in 56 hospitalized dogs, that the blood urea test is just one more bit of valuable information that can be pieced together with other significant findings in order to arrive at a diagnosis and prognosis. On the results of experimental studies and based on more than 1000 B.U.N. determinations, Allison, et al. (1) conclude that a B.U.N. over 23 mgm percent is due to nitrogen retention and kidney damage or from other abnormalities and that 'in general the higher the B.U.N. the

greater was the extent of kidney damage'.

Discussing the pathogenesis of uremia, Guild (23) paints a vivid picture of the residual healthy nephrons in a dog with chronic nephritis associated with high B.U.N. struggling valiantly although unsuccessfully to keep up with the excretion of minimal obligated daily load of chemical particles normally excreted in the urine. Platt quoted by Sodeman (52) emphasizes the same concept in his Lumlian lectures when he says 'our concept of renal failure should not be one of disordered functions, but rather one of extremely efficient function by renal remnant too small for its task'. The kidney, in addition to excreting the non-volatile end products of protein catabolism, coordinates with the lung in regulating the composition and volume of extra-cellular fluids and derangements of this function play a fundamental part in the pathogenesis of uremia (19). The pattern of N.P.N. in the plasma of five critically wounded soldiers was studied by Levenson, et al. (36) who found the urea concentrations were as much as 30 times the normal during the period of study extending from the day of injury to two weeks thereafter. Several of the blood electrolytes may show abnormalities in their concentrations in the uremic state. Although these variations are generally of little importance in the diagnosis, they are of significance in the treatment. The levels of some of the electrolytes of blood, including phosphates, sulphates, neutral sulphates, potassium and sometimes sodium are ordinarily increased in uremia, whereas others including chloride, calcium and sometimes sodium, are commonly diminished. In the uremic form of interstitial nephritis, there is frequently a decrease of blood chlorides, due largely to the associated vomiting. The determination of the chloride level is of particular value as an aid in the therapy of the dehydrated state

in this syndrome (9). Schwartz and colleagues (50) noticed significant quantities of bicarbonate are excreted in the urine by uremic subjects. The defect in the tubular reabsorption of alkali is responsible for this bicarbonate wasting and consequent development of acidosis in uremia. Discussing the calcium metabolism in uremia, de Wardener (16) is of the opinion that the process of decalcification in the bones occurs only in patients whose blood urea has been raised for a considerable time. These changes are not related to the plasma concentration of phosphorus or the presence of acidosis. There is no correlation between the blood level of calcium and phosphorus and the type of bone lesion although a majority of patients have a low calcium and an increased plasma phosphorus. The experimental data of Pierce and his co-workers (48) suggest that the peripheral arterial citrate concentration in uremic patients is elevated, that there is marked utilization of citrate by the peripheral tissues and that overproduction of citrate by the liver is responsible for the hypercitremia observed in uremia. Lewis, et al. (37) observed a bleeding tendency in uremia in 12 (Human) patients where abnormalities in the blood platelets were encountered. Larrain and Langdell (35) in their study on dogs with acute urinary retention and uremia following bilateral ligation of ureters, found the clotting time of blood was prolonged in these experimental animals. The cause of anemia in chronic renal failure is unknown. The main feature is a depression of bone marrow function directly proportional though not necessarily caused, by the rise in blood urea (16). Urea has been used as a feed supplement in cattle feeds. The bacterial flora in the rumen can synthesize protein from urea in presence of carbohydrates. However, toxicity arising from improper mixing or from the accidental feeding of large amounts of urea, especially

to ruminants that are unaccustomed to it, may cause serious death losses. Pierson and Aanes (48) have reported an outbreak of urea poisoning in a group of feedlot lambs resulting in acute circulatory collapse following venous stasis. The toxicity is attributed to ammonium carbamate, an intermediate compound in hydrolysis of urea by the bacterial flora in the rumen.

In the treatment of uremia attempts have been made by different workers to inhibit the nitrogen retention and to promote urinary excretion of the waste products of metabolism. Peritoneal lavage has proven successful in some cases. A lavage fluid approximating the electrolyte composition of the tissue fluids is injected into the peritoneal cavity to be removed later at varying intervals. The peritoneum acts as a dialyzing membrane. The benefit of this treatment is demonstrated by the reduction of B.U.N. levels from 275 mgm percent to 33 mgm percent. It is recommended that intermittent peritoneal lavage is a practical clinical procedure which can be used as a temporary substitute for the excretory functions of the kidney (30). This principle was extended to produce the 'artificial kidney' with its dialyzing system. Kolff (33) reviewing the usefulness of the artificial kidney concluded that, besides rapidly restoring the electrolyte composition of the blood plasma, the artificial kidney reversed the clinical picture of severe acute uremia within 24 hours, and in chronic cases it took two to four days to obtain optimum improvement. Desoxycorticosterone acetate (D.C.A.) was found to decrease the level of B.U.N. markedly from a pre-treatment level ranging from 160-330 mgm percent to the post-treatment level of 37-80 mgm percent in Dickson's (17) clinical studies on the treatment of uremia in dogs. The therapeutic response to D.C.A. is attributed to the increase in sodium retention and the increased potassium excretion, thus aiding in the clearing

of a potentially toxic product and further to the increased glomerular filtration, thus contributing to the reduction of azotemia. Mosier (42) concurs that the D.C.A. may produce a rather dramatic drop in the B.U.N. levels of uremic patients, if used with adequate fluid therapy. Testosterone may lower the blood urea level in uremic patients by diminishing protein catabolism and the effect, though small, is sufficient to justify the use of testosterone as an adjunct to other treatment of renal failure (20). In chronic uremia, where bone marrow depression is likely, a blood transfusion with a packed cell blood is recommended. This consists of allowing citrated blood to settle for 24 hours permitting the cells and plasma to separate. After the plasma is drawn off, only the cells are transfused; since most of the potassium passes into the plasma upon standing, a packed cell blood transfusion lessens the danger of potassium intoxication (28). Harris (24) studied the effect of Acutalyn R/ on 16 dogs of varying ages with chronic interstitial nephritis and toxemia and found decreased B.U.N. levels, urinary excretion of albumin and incidence of death. Mosier (42) stresses the importance of dietary regimen in uremia. Since renal pathology is the forerunner of uremia, the use of protein either as a food or as a hydrolysate should be reduced greatly to prevent the build-up of non-protein nitrogenous constituents in the blood. Most cases in which uremia has occurred, must be maintained on a life long diet of low quantity high quality protein.

From the literature reviewed, it is apparent that the kidney in addition to its excretory function, plays a significant role in homeostasis, that it is endowed with an enormous amount of functional tissue and that uremia is a complex resultant of a multiplicity of mechanisms set in motion by impaired renal function. There is a wide variation of the value of B.U.N.

both in health and disease. The importance of B.U.N. determination in diagnosis and prognosis of uremia cannot be overemphasized. In treating uremia the aim should be to prevent the build-up of nitrogenous waste and to promote urinary excretion of waste products of metabolism by appropriate and judicious therapeutic measures.

MATERIALS AND METHODS

A total of 27 dogs were used in this study. The dogs were of common breeds, ranging in age from four months to four years and weighing between 10 and 64 pounds. There were 11 males and 16 females.

All the dogs were kept under observation for a period of 24 hours preceding the experiments to record their general state of health as registered by the temperature, rate of pulse and respiration, condition of the visible mucous membrane, nature of appetite, character of secretions and excretions. Only those animals which were apparently healthy and whose B.U.N. ranged within normal limits were used for experimental study.

Determination of Blood Urea Nitrogen

The method of B.U.N. estimation followed in these experiments was the one recommended by Karr (29), utilizing the Klett-Summerson Photoelectric Colorimeter.

The Folin-Wu protein free filtrate was prepared by digesting two ml. of well-mixed heparinized blood with 16 ml. of N/12 sulphuric acid and two ml. of a ten percent sodium tungstate and filtered through a 9 cm., 40 Whatmann filter paper. One ml. of the filtrate then corresponded to one-tenth ml. of the original sample. Five ml. of the clear filtrate were

incubated with one drop of phosphate buffer and one drop of glycerol urease in a water bath at 50 degrees centigrade. The purpose of the buffer was to control the pH. of the solution, since the action of the enzyme was augmented at pH. 6.8. The enzyme urease decomposed the urea present and liberated ammonia which formed ammonium carbonate. After 15 minutes incubation, the contents were diluted to 25 ml. with distilled water. Ten ml. of this solution was transferred to the Klett-Summerson Colorimeter tube to which two drops of gum-ghatti solution had been previously added. Gum-ghatti was added to prevent the solution from becoming cloudy. One ml. of Koch-McMeekin Nessler's solution was then added and the contents mixed by inversion. The double iodide of mercury and potassium in the Nessler's solution reacted with ammonium carbonate to form a yellow dimercuric ammonium iodide. The depth of the color was measured in the Colorimeter at the end of ten minutes against a 0 of distilled water. To correct for the ammonia in the reagents particularly in the urease solution, the complete procedure of incubation with urease was repeated using five ml. of distilled water instead of protein-free filtrate. The Colorimeter reading of this blank was deducted from the unknown. A similar procedure was followed with a standard urea solution containing an equivalent of 45 mgm percent of B.U.N. with 1-10 filtrate. The B.U.N. was calculated against this standard solution as follows:

$$\frac{45}{\text{Reading of the standard minus Reading of the blank}} \times \text{Reading of the unknown minus Reading of the blank}$$

Surgical Technique

All the dogs in the experimental groups underwent surgery for the induction of uremia which was produced by artificial rupture of the bladder wall and allowing the urine to escape into the abdominal cavity to be re-absorbed through the peritoneum. The technique used in establishing the bladder tear was essentially the same as the one followed in performing Cystotomy.

Sodium pentabarbital was used to induce the general anesthesia and was given intravenously into the cephalic vein at the rate of one ml. for every five pounds body weight. The ventral aspect of the abdominal wall was shaved and the skin was thoroughly scrubbed with soap and water and the operative area bathed in an alcoholic solution of Roccal R/*. The dog was secured in dorsal recumbency and four large sterile towels were placed, one on each side of the proposed incision and fastened to the skin with Backhaus towel clamps. In the male a paramedian incision four inches long was made over the lower part of the rectus abdominis muscle, just lateral to the penis. In the female, the incision extended from below the umbilicus to the pubis in the midline. The incision passed through the muscular coat and the peritoneum. At this time the bladder was exposed to the full view. The fundus of the bladder was lifted into the wound with a pair of Allis forceps and an incision one and a half inches long was made into the bladder and an elliptical piece of the wall of the same length was removed. The capillary hemmorrhage resulting from the incision was arrested by pressure

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*Roccal R/ is Benzalkonium chloride from Winthrop Laboratories, New York 18, New York.

with artery forceps. The bladder was returned to the abdominal cavity. The muscular layer of the abdomen including the peritoneum was approximated by interrupted sutures with Vetafil R/**, size 0.30 mm. The skin wound was closed separately using interrupted sutures of the same material.

In the second and fourth groups surgical repair of the bladder defect was performed 24 hours later. The accumulated urine in the abdominal cavity was drained by suction with a hypodermic syringe and the bladder was lifted to the abdominal wound. The defect made earlier in the wall of the bladder was located, its edges freshened and the breach was closed by continuous Lembert sutures with an atraumatic needle and 00 chromic catgut. The bladder was returned to the abdominal cavity and the wall of the abdomen repaired in the orthodox manner.

The technique of operation was the same for the control group (Group five), but the bladder was not ruptured in these cases.

Experimental Procedure

The 27 dogs used in these experiments were picked up at random and divided into five groups.

Group one consisted of six dogs, experimental numbers 1, 3, 4, 5, 6 and 14. There were three males and three females ranging in age from six months to four years and weighing between 11 and 64 pounds. These underwent surgery for the induction of uremia by the technique described above. During the next 72 hours, the symptoms were recorded, a blood sample was drawn every 12 hours and the B.U.N. estimated.

**Vetafil R/ is from Bengen and Co., Hannover, Germany.

Five dogs, experimental numbers 2, 7, 8, 9 and 10, belonging to group two consisting of two males and three females ranging in age from one to two years and weighing between 18 and 32 pounds passed through the experimental procedures followed in group one. However the defect created in the bladder wall was repaired at the end of 24 hours.

Group three included eight dogs, experimental numbers 15, 16, 17, 18, 19, 20, 26 and 27 comprising three males and five females ranging in age from four months to three years and weighing between 10 and 46 pounds in whom uremia was experimentally produced as in group one. In addition these animals received five ml. of Acutalyn R/* intravenously before surgery. One half the dose, 2.5 ml., was repeated 24 hours later and continued every 12 hours thereafter.

Experimental procedures in group two were repeated for dogs, experimental numbers 11, 12, 13, 21, 22, and 23 in group four. There were one male and five females in this group ranging in age from six months to two years and weighing between 18 and 42 pounds. In addition these received Acutalyn R/ in the same manner as dogs in group three.

Control for groups one and two was experimental number 24 dog from group five which passed through the same period of observation as the dogs belonging to the groups one and two. This was a male terrier aged two years and weighed 20 pounds. The operative technique for this animal was the same as those in the above experimental groups but the bladder was not ruptured in this case. The B.U.N. was estimated every 12 hours.

Control for groups three and four was a male dog, experimental number 25,

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*Acutalyn R/ from Enzyme Products, Inc., Palo Alto, California.

aged three years. He weighed 26 pounds. The experimental procedures on control 24 were duplicated in this animal. In addition this dog received Acutalyn R/ intravenously on the same dosage schedule adopted for the experimental animals belonging to groups three and four.

RESULTS OF EXPERIMENTATION

Experimental Production of Uremia

All the six experimental dogs of group one recovered from the anesthesia in the course of six to 12 hours. They demonstrated intense thirst and readily consumed water. The appetite was unimparied. By the 18th hour following surgery, they became dull and apathetic, refused food, but continued to drink large quantities of water. Immediately there was nausea, retching and the whole quantity of water mixed with mucus and remnants of food was emitted. The nausea, retching and vomition became incessant and violent thereafter. Experimental dog number 1 vomited blood tinged bile at the height of uremia. The animals became rapidly dehydrated, wore a haggard expression and by the 36th hour, the symptoms of uremia were well established. The pulse was at first frequent and full, but became wiry and imperceptible towards the terminal stages of the disease. The conjuntiva was injected. There was frequent ineffective efforts at micturition. The abdomen was tucked up and palpation of the abdomen resented. No stomatitis was noticed, but the ammoniacal odor of the breath was present. There was fetid, watery, blood tinged diarrhea. As the disease progressed and the general condition deteriorated, the animals became somnolent and gradually lapsed into coma. Death occurred in all the cases at varying intervals between 36 and 72 hours following surgery. The animals remained

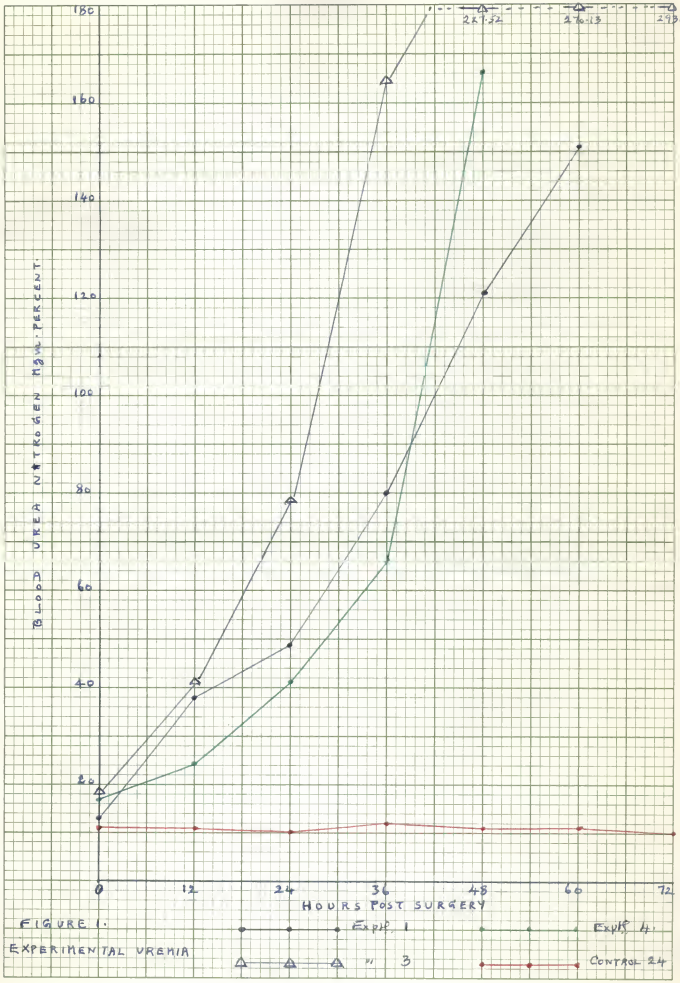

FIGURE 1:
EXPERIMENTAL UREMIA

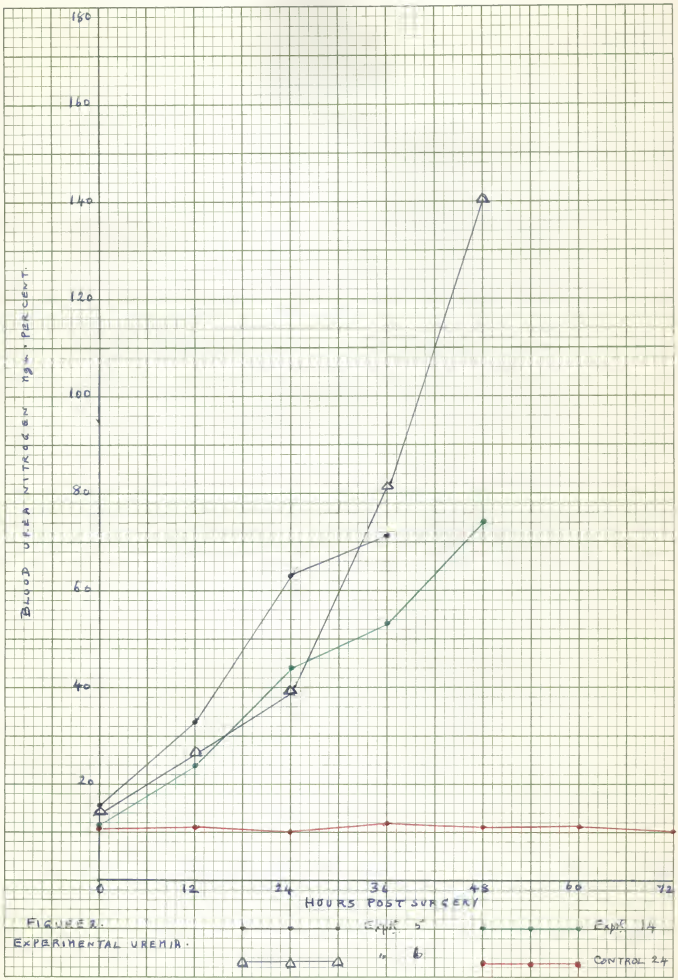

FIGURE 2.
EXPERIMENTAL UREMIA.

Table 2. Blood urea nitrogen in experimental uremia.

Serial No.	Experimental No.	Weight	B.U.N. Mgm % before surgery	B.U.N. Mgm % post surgery 12 hrs.	24 hrs.	36 hrs.	48 hrs.	60 hrs.	72 hrs.	Result
1	1	20	13.08	37.85	49.07	79.97	120.56	151.40	—	Died
2	3	11	18.25	41.48	78.21	163.53	227.52	270.13	293.89	Died
3	4	64	16.59	23.70	41.48	65.89	165.90	—	—	Died
4	5	62	14.93	33.18	62.57	71.10	—	—	—	Died
5	6	24	14.22	26.07	39.11	80.58	139.83	—	—	Died
6	14	38	10.50	24.00	43.75	52.50	73.75	—	—	Died
Average			14.60	31.05	52.37	85.60	145.51	210.77		
Control	24	20	11.00	10.80	10.25	11.52	11.45	10.85	10.45	Survived

afebrile during the course of the experiment. Uremic convulsions were not observed in any of these cases. The onset of uremia was evident by polydipsia in all the cases as early as the 18th hour following rupture of the bladder. In experimental dog number 5 the symptoms were well marked by the 24th hour and death occurred 12 hours later. In other cases the symptoms were well established between 24-36 hours. Experimental dog number 3 survived for 72 hours. Death occurred in experimental dogs numbers 4, 6, and 14 at the end of 48 hours. There was a progressive rise in the level of B.U.N. in all the cases with a sudden elevation between the 24th and 48th hour in experimental dogs numbers 3, 4 and 6. The highest level was recorded by experimental dog number 3 just prior to death. (293.89 mgm%)

Necropsy was conducted on experimental dogs numbers 1, 4, 5, 26 and 27. Lesions noted included the presence of blood tinged urine in the abdominal cavity, and congestion of the liver, spleen and kidneys. The bladder defect was present and showed a zone of congestion around the periphery of the tear. Examination of the gastro-intestinal tract revealed catarrhal changes throughout with semi-fluid contents containing mucus and blood. No evidence of ulceration was noted.

Experimental Production of Uremia and Subsequent Repair of the Bladder Tear

Experimental dogs numbers 2, 7, 8, 9 and 10 belonging to group two underwent surgery for experimental induction of uremia as in group one. During the next 24 hours, there was a rise in the level of B.U.N. Animals were dull and exhibited polydipsia, nausea and vomition. Before the symptoms became violent and alarming, a laparatomy was performed and the

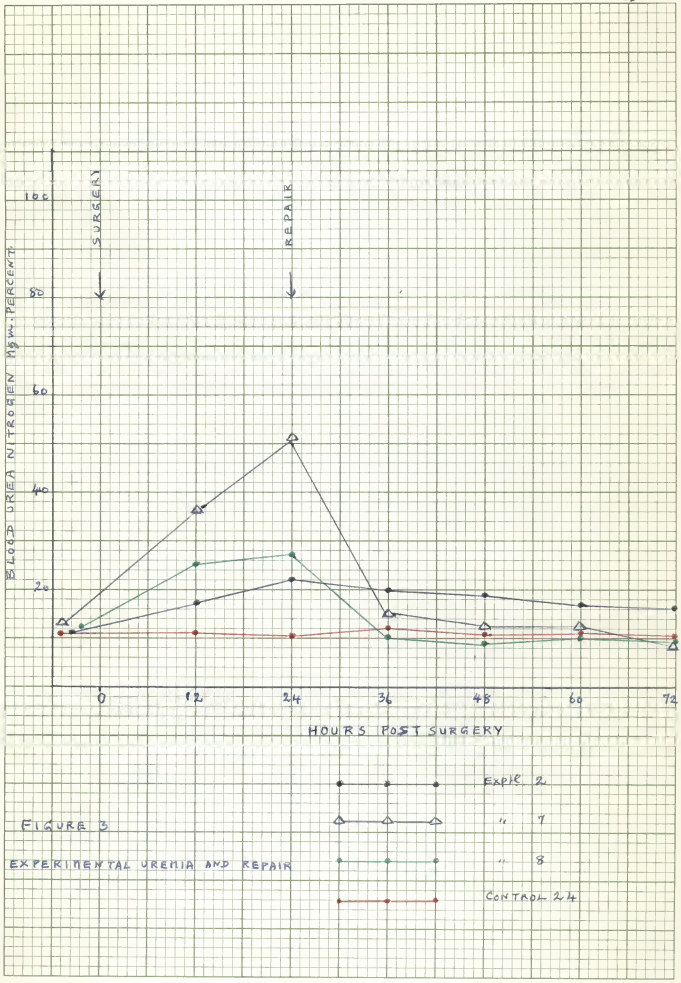

FIGURE 3

EXPERIMENTAL UREMIA AND REPAIR

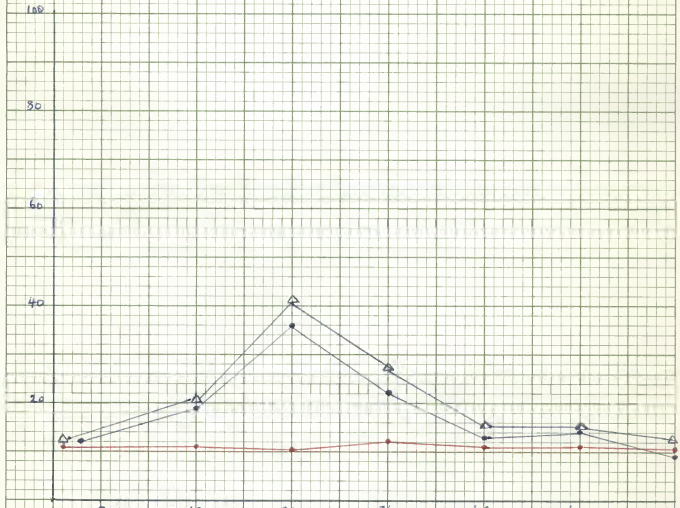

FIGURE 4:

EXPERIMENTAL UREMIA AND REPAIR

EXPT'L 9

" 10

CONTROL 24

Table 3. Blood urea nitrogen after surgical repair of the bladder defect in experimentally induced uremia.

Serial No.	Experimental No.	Experimental Weight	B.U.N. Mgm % before surgery	Blood Urea Nitrogen Mgm % Post surgery: Before Repair 12 hrs.	Before Repair 24 hrs.	After repair of the bladder defect 36 hrs.	After repair of the bladder defect 48 hrs.	After repair of the bladder defect 60 hrs.	After repair of the bladder defect 72 hrs.	Result
1	2	32	11.22	17.29	22.43	20.09	18.69	16.82	15.89	Survived
2	7	20	12.80	35.55	50.72	15.17	11.85	11.85	8.30	Survived
3	8	24	12.32	24.89	27.49	9.95	9.48	9.62	9.01	Survived
4	9	18	11.85	18.96	35.55	21.80	13.27	14.22	9.48	Survived
5	10	20	12.32	20.15	41.48	27.26	15.41	14.22	11.85	Survived
Average			12.10	23.37	35.53	18.95	13.74	13.35	10.91	
Control	24	20	11.00	10.80	10.25	11.52	11.45	10.85	10.45	Survived

bladder defect repaired in each case. Within 12 hours the animals showed a dramatic improvement and there was a rapid fall in the level of B.U.N. to within the normal range. Thus, further development of uremia was completely suppressed in these animals and by the third day all were well on the road to recovery. After seven days of observation they were discharged. The B.U.N. rose to 50.72 mgm percent at the end of 24 hours following rupture of the bladder in experimental dog number 7. In experimental dogs 9 and 10 it ranged between 35 and 42 mgm percent and in others it was under 30 mgm percent.

Acutalyn R/ in Experimentally Induced Uremia

Acutalyn R/ given intravenously at the dosage schedule previously described was found to delay the onset of uremia, though it was not able to halt the fatal culmination of the syndrome. All the animals exhibited comparatively milder symptoms during the first 24 hours. However, their general condition deteriorated thereafter and death occurred in acute uremia in all the cases except in experimental dog number 16, at varying intervals between 60 and 84 hours. Experimental dog 16 died 48 hours following surgery. The levels of B.U.N. did not rise above 33 mgm percent during the 24 hours following surgery and although there was a progressive increase in the B.U.N., the peak levels were lower than in group one. The highest level of B.U.N. recorded was in experimental dog number 17, 138.50 mgm percent.

Acutalyn R/ and Repair of the Bladder Defect in Experimental Uremia

In this group it was found that all animals rapidly recovered from the initial mild symptoms of uremia. Acutalyn R/ apparently controlled the uremic

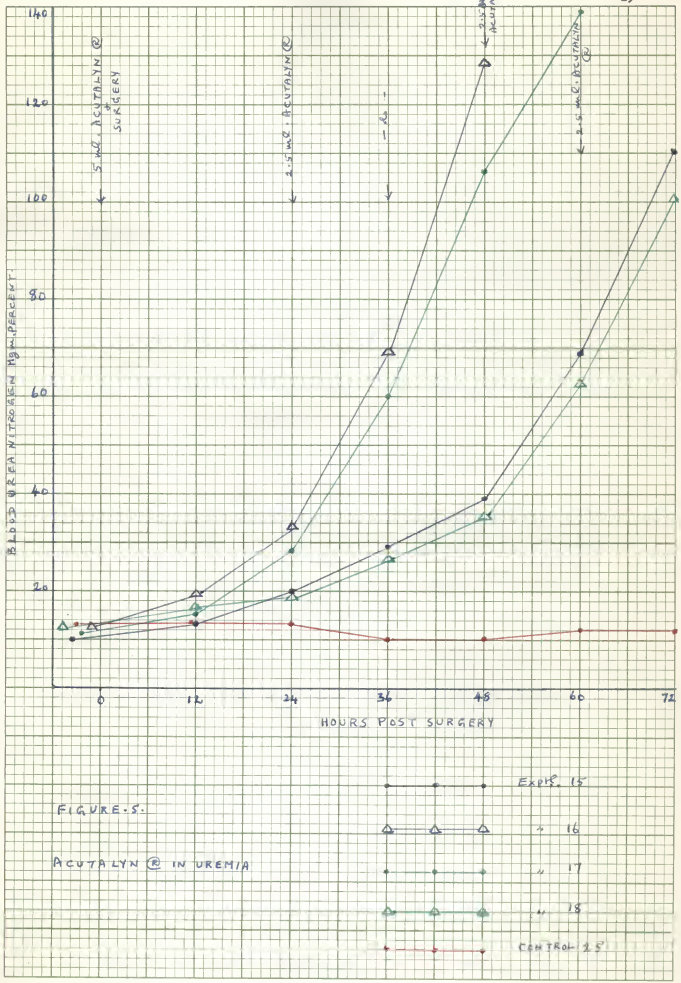

FIGURE-5:

ACUTALYN ® IN UREMIA

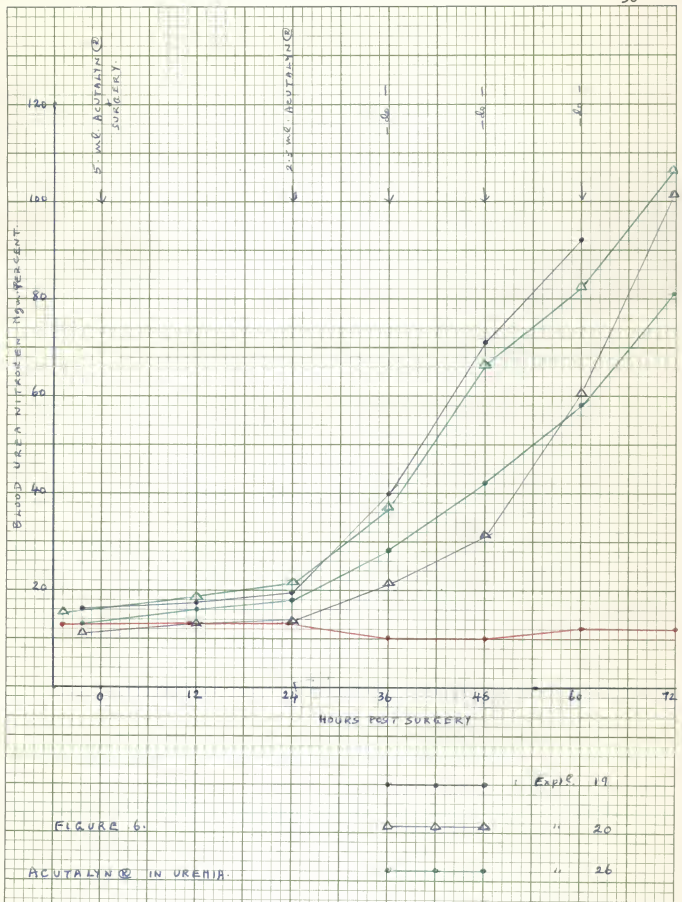

FIGURE 6:

ACUTALYN ® IN UREMIA.

Table 4. Acutalyn R/* in experimental uremia.

Serial No.	Experimental No.	Weight in lbs.	B.U.N. Mgm % before surgery	B.U.N. Mgm % Post surgery 12 hrs.	24 hrs.	36 hrs.	48 hrs.	60 hrs.	72 hrs.	Result
1	15	46	10.00	13.00	20.00	28.75	38.75	63.50	110.00	Died
2	16	10	11.75	18.50	32.50	68.75	127.50	—	—	Died
3	17	16	11.00	15.00	28.25	60.00	106.25	138.50	—	Died
4	18	21	12.25	15.50	18.00	26.00	35.25	62.25	100.25	Died
5	19	22	15.75	17.00	18.75	39.75	70.50	91.75	—	Died
6	20	29	11.25	12.50	13.25	21.22	31.20	59.75	101.25	Died
7	26	36	12.75	16.25	17.50	28.00	42.25	57.50	81.25	Died
8	27	16	15.00	18.25	20.50	36.75	65.50	82.25	106.25	Died
Average			12.47	15.69	21.09	38.65	64.65	80.07	99.80	
Control	25	26	12.50	13.25	12.50	10.25	9.75	11.50	12.25	Survived

* 5 ml. Acutalyn R/ at the time of surgery.
2.5 ml. 24 hours later and repeated every 12 hours thereafter.

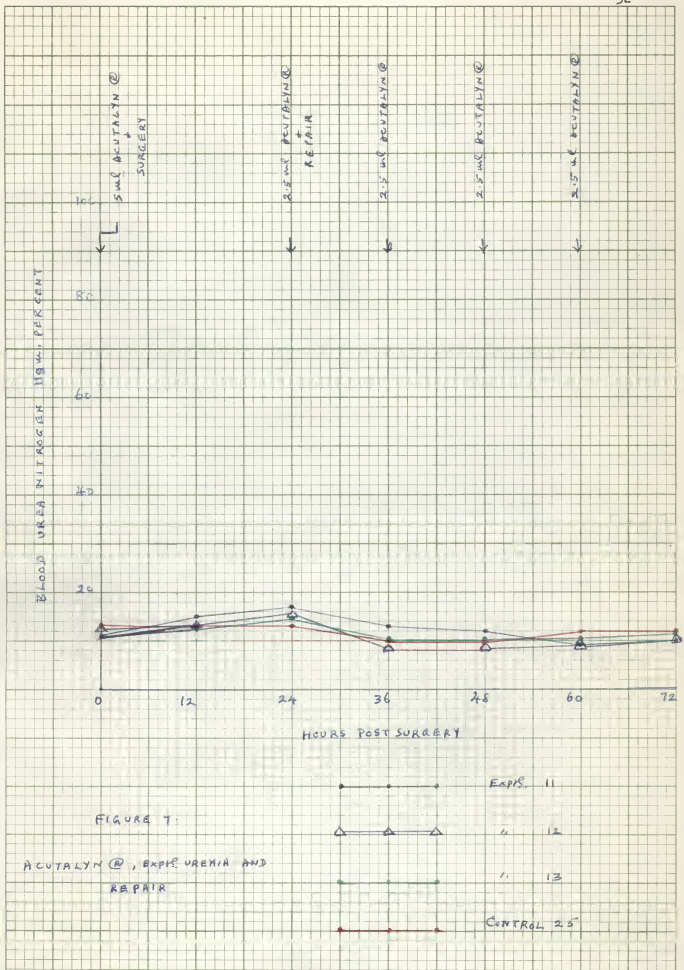

FIGURE 7

ACUTALYN @, EXPTL UREMIA AND REPAIR

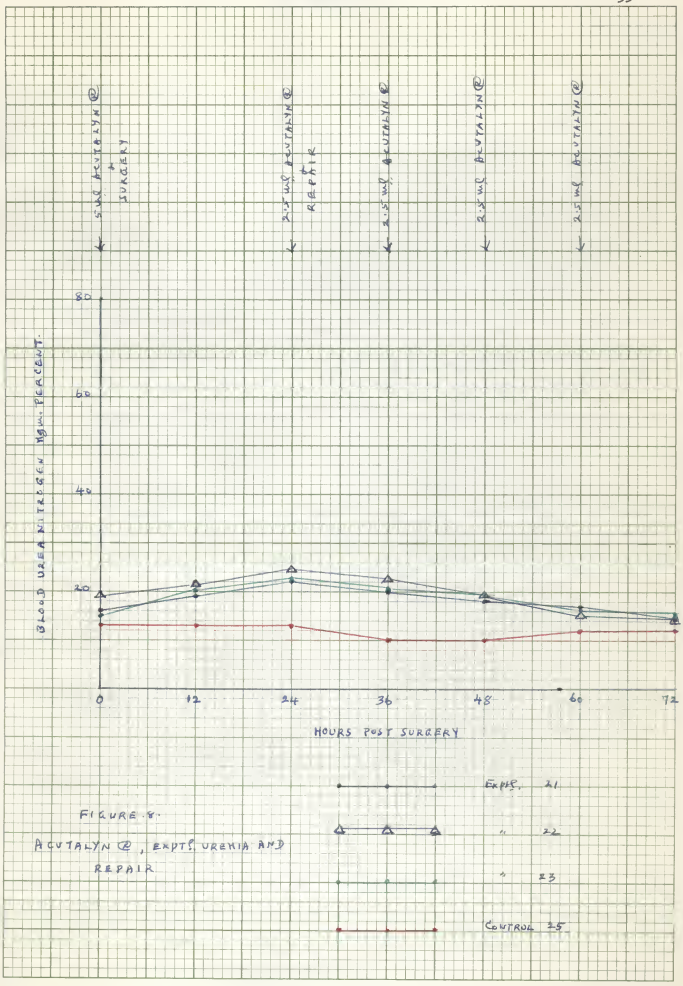

FIGURE 8.

ACUTALYN®, EXPTL. UREMIA AND REPAIR

Table 5. Effect of Acutalyn R/* and repair on B.U.N. in experimentally induced uremia.

Serial No.	Experimental No.	Weight	B.U.N. Mgm % before surgery	Blood urea nitrogen Mgm % post surgery: Before Repair 12 hrs.	24 hrs.	After repair of the bladder defect 36 hrs.	48 hrs.	60 hrs.	72 hrs.	Result
1	11	27	10.67	15.41	16.59	12.80	11.85	9.01	9.82	Survived
2	12	18	12.32	13.27	14.52	8.06	7.82	9.48	10.22	Survived
3	13	42	11.38	12.80	15.41	9.95	10.12	11.85	11.38	Survived
4	21	22	16.25	18.75	21.50	19.75	18.25	17.00	14.00	Survived
5	22	20	18.50	21.00	24.25	21.50	19.00	15.00	13.50	Survived
6	23	26	15.00	19.50	22.00	20.25	18.75	15.50	14.50	Survived
Average			14.02	16.79	19.01	15.42	14.30	12.97	12.24	
Control	25	26	12.50	13.25	12.50	10.25	9.75	11.50	12.25	Survived

* 5 ml. Acutalyn R/ at the time of surgery.
2.5 ml. 24 hours later and repeated every 12 hours thereafter.

changes in the tissues as well as the level of urea nitrogen in the blood. When further absorption of urinary waste products was prevented by repair of the bladder defect, all the animals made an uneventful recovery under the protective influence of this drug. The B.U.N. dropped to within normal range within 24 hours following repair.

Control dog, experimental number 24, recovered from the laparotomy procedure without apparent difficulty. The B.U.N. ranged within normal limits, from 10.25 mgm percent to 11.52 mgm percent. After seven days observation he was discharged.

Acutalyn R/ given to control dog, experimental number 25, prior to surgery and repeated as per the schedule adopted for the experimental animals belonging to groups three and four, had no significant effect on the B.U.N. though clinically he had a comparatively shortened recovery phase following surgery. The B.U.N. ranged from 9.75 mgm percent to 13.25 mgm percent in this animal.

DISCUSSION

Crandall (13) in his discussion concerning the high levels of B.U.N. in hospitalized dogs listed the several factors to be taken into consideration in evaluating the B.U.N. as a diagnostic aid. The amount of protein ingested, the volume of urine excreted, the destruction of body protein and the impairment of renal functions were particularly stressed. He further suggested that house broken dogs which were kept in the hospital kennels might retain their urine for long period of time, causing stony of the bladder with abnormal retention and consequent reabsorption of metabolites into the system.

Based on his observation all the dogs used in this study, experimental dogs number 1 to 27, were kept under optimal conditions of hospital management

for several days prior to the commencement of the experiments. They received a prepared balanced food supplied by the Gaines Food Products, Inc. Adequate water was provided for all the animals utilized. They were taken out of the kennels daily and exercised. A clinical examination revealed these dogs to be apparently healthy. The B.U.N. was estimated at the same time each day, and was found to be within normal range. The highest value, 18.50 mgm percent, was shown by experimental dog number 22 and the lowest, 10.00 mgm percent by experimental dog number 15, with an average of 13.15 mgm percent for the 27 dogs. These figures were in close agreement with those obtained by previous workers, Table 1.

Following surgery, all the dogs in group one showed acute symptoms of uremia and died in the course of 36-72 hours. A progressive rise in the level of B.U.N. accompanied by an increase in the severity of the symptoms was noted. The rapid elevation in the B.U.N. levels between 24-48 hours in experimental dogs 3, 4 and 6 was significant and should be regarded as the warning signal to institute surgical measures for early repair of the bladder tear in naturally occurring cases. The acute course of the disease might account for the absence of typical lesions of the disease as described in text books. Probably sufficient time was not allowed for the 'uremic toxin', whatever its nature might be to exert the pathogenic effect on the tissues.

In evaluating the B.U.N. following surgery in these dogs, several points were taken into consideration. The degree of distention of the bladder at the time of rupture, the volume of urine that escaped into the abdominal cavity, the patency of the defect, and the volume of water and quantity of food ingested during the post operative period were carefully observed.

Variation of any one of these factors might influence the level of B.U.N. in experimental work of this nature. In all the experimental animals, 1 to 23, 26 and 27 the bladder was found to be partially filled with urine at the time of surgery and approximately 40-50 ml. of urine escaped into the abdominal cavity at the time of rupture of this organ. At necropsy on dogs, experimental numbers 1, 4, 5, 26 and 27, the bladder defect was found to be patent with extravasation of blood-tinged urine in the abdominal cavity. All the dogs in the second and fourth groups showed a similar picture at the time of repair of the bladder wall. During the first six hours following recovery from the anesthetic the animals in group one consumed food and water. Following this period there was a progressive anorexia, nausea and vomition resulting in rapid dehydration and death due to acute uremia. From the observations made on the symptomatology and the pattern of B.U.N. in these dogs, it might be concluded that a B.U.N. over 40 mgm percent was of diagnostic importance in acute uremia.

Repair of the bladder defect at the end of 24 hours, before the symptoms of uremia were well established, brought about a rapid decrease in the level of B.U.N. from the average peak of 35.53 mgm percent to an average of 18.95 mgm percent in 12 hours in five cases in group two. During the next 36 hours all the animals in this group recovered completely. Experimental studies in this series had shown the prognostic significance of B.U.N. in uremia. It was apparent that the alarming symptoms of uremia developed simultaneously with the rapid increase in B.U.N. and that the repair of the damage to the bladder wall brought about an ameliorating effect on the general condition of the patient with the concomitant drop in the level of B.U.N. Following accidental rupture of the bladder a determination of B.U.N. would definitely

aid in assessing the condition of the patient for surgery. The pattern of B.U.N. curves in Fig. 1 would indicate that even if the operation were delayed by 24 hours the chances of recovery after surgical repair would be reasonably bright. Beyond 36 hours, the condition of the animals was such that there would be little hope of recovery even though surgery was performed.

In the third and fourth series of experiments, the effect of Acutalyn R/ on experimentally produced uremia was studied.

The effect of Acutalyn R/ against various drug intoxication had been well documented by experimental evidence. Mosier (14) has been credited to be the first to report on the beneficial effect of this drug in cases of uremia in dogs. However, the use of Acutalyn R/ in extreme cases had not influenced the mortality and autopsy findings in these cases usually revealed irreversible or overwhelming parenchymal damage. Subsequent reports of Harris (24) and Cascinai (14) have substantiated the above findings. It was also found that Acutalyn R/ when given prior to surgery had the normalizing effect on the B.U.N. levels and improved the well being of the patient during the post-operative period.

In the third series of the study Acutalyn R/ did control the level of the B.U.N. during the initial stage of the disease and although it delayed the onset of clinical uremia in experimental dogs, numbers 15, 16, 17, 18, 19, 20, 26 and 27 it did not halt the fatal culmination of the disease in these animals. In fact after 24 hours following the creation of the bladder defect the B.U.N. rose at a rapid rate and all the animals succumbed to the disease in the course of 48-84 hours, Table 4. Probably the biochemical changes and the tissue damage progressed to an irreversible stage at such a pace that continued administration of the drug failed to exert any

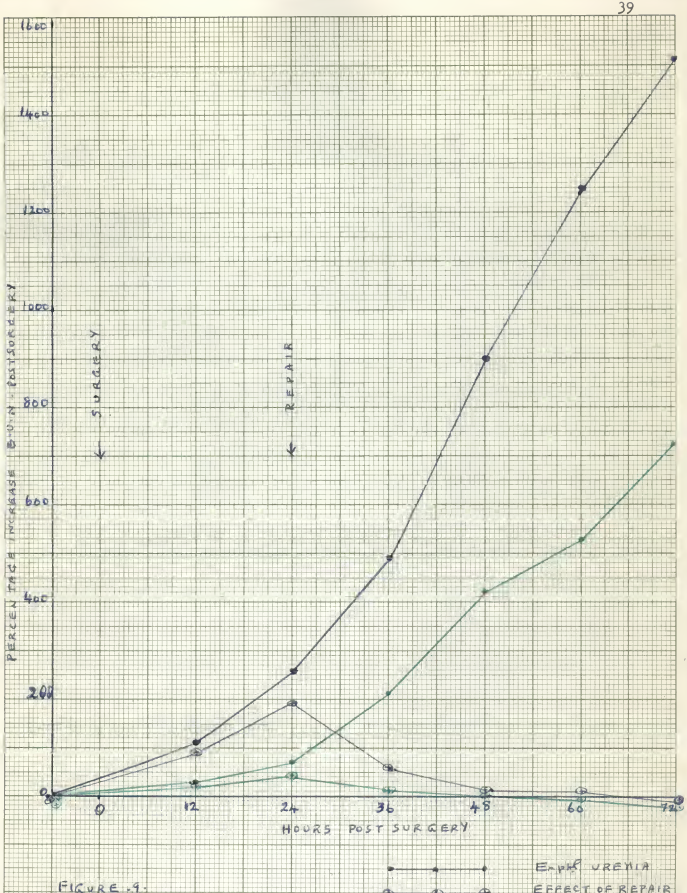

FIGURE. 9.

PERCENTAGE INCREASE BUN; POST SURGERY, REPAIR & ACUTALIN®

Table 6. Percentage increase in B.U.N., post surgery, repair and with Acutalyn R/.

Serial No.	Experimental	Average B.U.N. Mgm %	Percentage increase post surgery						Results
			12 hrs.	24 hrs.	36 hrs.	48 hrs.	60 hrs.	72 hrs.	
1	1. Series--uremia	14.60	112.7	258.7	486.3	901.4	1245.11	1510.4	All died
2	2. Series--uremia and repair	12.10	93.1	193.7	56.6	13.6	10.3	Normal	All survived
3	3. Acutalyn R/ in uremia	12.47	25.8	69.1	209.9	418.4	531.5	714.7	All died
4	4. Series Acutalyn R/ and repair in uremia	14.02	19.8	35.6	10.0	2.0	Normal	Normal	All survived

appreciable effect either on the rise of B.U.N. or the severity of the symptoms. The cause of the steep rise of B.U.N. in experimental dogs numbers 16 and 17 was not determined.

The fourth series of experiments demonstrated the combined effect of Acutalyn R/ and the surgical repair of the bladder defect on experimentally induced uremia. Acutalyn R/ controlled the toxemia until further absorption of urinary waste products was prevented by surgical repair of the bladder defect. All the animals in this group, experimental numbers 11, 12, 13, 21, 22 and 23, made a rapid recovery during the course of 24 hours following the surgical repair. Early surgical repair alone did bring about a satisfactory cure of the condition as seen in the second series of experiments, Figs. 3 and 4. However, the shorter crest in the percentage increase of B.U.N. shown in Fig. 9 compared to the one shown in case of repair (in the same figure), correlated with the clinical observations would definitely establish the efficacy of Acutalyn R/ in suppressing the B.U.N., in controlling the early shock during surgery in these animals and perhaps in counteracting the biochemical changes in the tissues to bring about a dramatic recovery from acute uremia.

SUMMARY

An acute rapidly fatal uremia was experimentally induced by producing a defect in the bladder wall in normal healthy dogs.

The highest level of B.U.N. in experimentally induced uremia was found to be 293.89 mgm percent.

The onset of uremia in these animals was evident by the 18th hour following surgery and by the 36th hour the symptoms of uremia were well

established. All the animals succumbed to the disease in the course of 72 hours.

The rapid rise in the B.U.N. level in experimental dogs, numbers 3, 4 and 6 between 24-48 hours was significant and might be of prognostic importance in the naturally occurring cases of rupture of this organ. After 36 hours such animal would definitely be a poor surgical risk.

Following surgical repair, there was a rapid fall in the level of B.U.N. and a return to a general wellbeing of the patient.

Administration of Acutalyn R/ delayed the onset of uremia though after 24 hours it had no appreciable effect on the course of the disease or the pattern of B.U.N. rise.

Acutalyn R/ prevented the development of the uremic syndrome in dogs with bladder defects when the defect was repaired within 24 hours of its experimental production.

It was found the B.U.N. ranged from 10.00 mgm percent to 18.50 mgm percent with an overall average of 13.15 mgm percent in normal 27 healthy dogs during hospitalization.

ACKNOWLEDGMENTS

Grateful acknowledgment to Dr. J. E. Mosier, major instructor, who suggested the problem and who gave valuable counsel, encouragement and guidance during this study.

Acknowledgment to Dr. E. H. Coles, Department of Pathology, for his advice and for the use of laboratory facilities.

Thanks are due to Dr. E. J. Frick, Head of the Department of Surgery and Medicine for the facilities afforded in the clinic and to Dr. Larson of the same Department for his helpful suggestions during the course of this study.

Sincere thanks are due to the Enzyme Products, Inc., who provided a generous supply of Acutalyn R/ used in this study.

BIBLIOGRAPHY

1. Allison, J. B., H. O. Dreskin, and M. L. Morris.
Data and bibliography on some nitrogenous constituents of normal dog's blood. Amer. Jour. Vet. Res., 1:197. 1940-41.

2. Anninuo, J. S.
Clinical Chemistry - Principles and procedures. 1st ed. Boston: Little, Brown. 1956.

3. Armistead, W. W.
Canine medicine. 2nd ed. California: American Veterinary Publications, 1959. 29 p.

4. Best, Charles Herbert and Norman Burke Taylor.
The physiological basis of medical practice. 6th ed. Baltimore: Williams and Wilkins, 1955. 479 p.

5. Bild, C. E.
Technique of determining blood urea percentage. Vet. Med., 50:133-135. 1955.

6. Bloom, Frank.
Pathology of dog and cat. Evanston, Ill.: American Veterinary Publications, 1954. 89 p.

7. _____.
Pathology of dog and cat. Evanston, Ill.: American Veterinary Publications, 1954. 168 p.

8. _____.
Canine medicine. California: American Veterinary Publication, 1959. 194 p.

9. _____.
The laboratory diagnosis of interstitial nephritis in the dog, Part 2. The North Amer. Vet. 38:244-248. 1957.

10. Bollman, J. L., and F. C. Mann.
Nitrogenous constituents of blood following transplantation of ureters into different levels of intestines. Proc. Soc. Exp. Biol. Med., 24:923. 1927.

11. Bodil, Schmidt-Nielsen.
Urea excretion in mammals. Physiological Reviews. 38:139-168. 1958.

12. Coffin, D. L., and V. J. Cabasso.
The blood and urine findings in infectious canine hepatitis. Amer. Jour. Vet. Res. 14:254-259. 1953.

13. Crandall, N. D.
A survey of blood urea levels in hospitalized dogs. Auburn Veterinarian. 5:108. 1949.

14. Data Brochure on the metabolic normalizing aspects of Acutalyn. Enzyme Products, Inc. Palo Alto, California.

15. Davies, G. K.
Urea in cattle feeds. Vet. Med., 51:154. 1956.

16. deWardener, H. E.
The kidney - An outline of normal and abnormal structure and function. Boston: Little, Brown, 1958.

17. Dickson, M. W., and R. L. Ott.
Desoxycorticosterone acetate in the treatment of uremia in dogs. Vet. Med. 50:451-455. 1955.

18. Ershoff, B. H.
Comparative effects of liver and yeast on growth and length of survival of the immature thyroid-fed rats. Arch. Biochem. 15:365. 1947.

19. Fishberg, Arthur M.
Hypertension and nephritis 5th ed. Philadelphia: Lea and Febiger, 1954.

20. Freedman, P., and A. G. Spencer.
Testosterone propionate in the treatment of renal failure. Clin. Sci. 16:11-22. 1957.

21. Grace, V. H., et al.
Experimental uremia in young pigs. Amer. Jour. Vet. Res. 12:206. 1951.

22. Grimm, E. A.
Uremia associated with renal calculi and nephritis in a dog. J. A. V. M. A. 130:224. 1957.

23. Guild, W. R.
Chronic uremia in dogs. J.A.V.M.A. 134:276-279. 1959.

24. Harris, T. D.
The effect of new active hepatic principle in the treatment of chronic interstitial nephritis and toxemia. The California Veterinarian, 13:14-15. 1959.

25. Hawk, Phillip B., Bernard L. Oser, and William H. Summerson.
Practical physiological chemistry. 13th ed. New York: Blackiston, 1954. 545 p.

26. Herman, Leon.
The practice of urology. Philadelphia: W. B. Saunders, 1943, 399 p.

27. Hewlett, A. W., Q. O. Gilbert, and A. D. Wickett.
The toxic effects of urea on normal individuals. Arch. Int. Med., 9:329. 1924.

28. Huff, R. W., and P. T. Pearson.
Treatment of canine nephritis. J.A.V.M.A. 131:101-104. 1959.

29. Karr,
Blood urea nitrogen determination by colorimetric method. J. Lab. Clin. Med., 9:329. 1924.

30. Kirk, R. W.
Peritoneal lavage in uremia in dogs. J.A.V.M.A. 131:101-104. 1957.

31. _____.
The therapeutics of canine 'uremia'. 8th Gains Veterinary Symposium, Winter 1958-59.

32. Kirk, R. W., et al.
Canine medicine. 2nd ed. California: Amer. Vet. Publ., 1959, 194 p.

33. Kolff, W. J.
The artificial kidney - past, present and future. Jour. Biol. Abst., 31:2245. 1957.

34. Kolmer, John A.
Clinical diagnosis by laboratory examinations. 1st ed. revised. New York: Appleton Century, 1944. 719 p.

35. Larrain, C. and R. D. Langdell.
The hemostatic effect of uremia. Jour. Hematology. 11:1067-1072. 1956.

36. Levenson, S. M., J. M. Howard, and Rosen Hymen.
Studies on plasma amino acids and amino conjugates in patients with severe battle wounds. Biol. Abstracts. 30:2202. 1956.

37. Lewis, J. A., B. M. Zucker, and J. H. Ferguson.
Bleeding tendency in uremia. Jour. Hematology. 11:1073-76. 1956.

38. Leiter, L.
Observations on the relation of urea to uremia. Arch. Int. Med., 28:330. 1921.

39. Meyer, K. F., B. Stewart-Anderson, and B. Eddie.
Canine leptospirosis in the United States. Jour. Amer. Vet. Med. Assn., 95:710. 1939.

40. Middleton, W. S.
The changing emphasis in the management of renal diseases. Post-graduate Medicine. 11:371-382. 1952.

41. Mosier, J. E.
Leptrospirosis of pet animals. Vet. Med. 52:537-39. 1957.

42. _____.
Treatment of leptospirosis of pet animals. Vet. Med. 52:546. 1957.

43. _____.
Efficacy of Acutalyn R/ in cases of uremia in dogs. Personal communication.

44. Mosier, J. E., and E. H. Coles.
Urinary tract infection of small animals. Vet. Med. 53:649. 1958.

45. Peters, J. P., and D. D. VanSlyke.
Quantitative clinical chemistry. Vol. 1 2nd ed. Baltimore: Williams and Wilkins, 1946. 631 p.

46. Phillips, L. R.
B.U.N. level in dogs. Personal communication.

47. Pierce, J. M., R. G. Warren, and J. P. Merril.
Citrate metabolism in uremia. Jour. Appl. Physiology. 11:231-37. 1957.

48. Pierson, R. E., and W. A. Aanes.
Urea poisoning in ruminants--report of a case in feed lot lambs. The Allied Veterinarian. 30:136-139. 1959.

49. Schnelle, G. B.
Clinical interpretations of laboratory reports. The North Amer. Vet. 31:600-607. 1950.

50. Schwartz, W. B., et al.
On the mechanism of acidosis in chronic renal diseases. Jour. Clin. Invest. 38:39-52. 1959.

51. Smith, K. W.
Some clinical aspects of canine nephritis. Vet. Med. 50:21. 1955.

52. Sodeman, William A.
Pathologic Physiology. 2nd ed. Philadelphia: W. B. Saunders, 1958.

53. Theobald, A. R.
Canine urology and urologic diagnosis in practice. North Amer. Vet. 20:48-51. 1959.

54. Thomas, E. F.
Hench-Aldrich test for blood urea. Vet. Med. 49:66. 1954.

A STUDY OF THE EFFECTS OF ACUTALYN R/ ON THE EXPERIMENTALLY INDUCED UREMIA IN CANINES

by

MAHARAJAPURAM SUBRAMANIA GANAPATHY

B. V. Sc., Madras University, 1940

AN ABSTRACT OF A THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Surgery and Medicine

KANSAS STATE UNIVERSITY
OF AGRICULTURE AND APPLIED SCIENCE

1960

The occurrence of vesical injuries are not uncommon in man and animals. Reabsorption of urinary waste products through the peritoneum should produce an elevated B.U.N. in these patients with rupture of the urinary bladder. Yet no data was available as to the incidence of uremia in natural or induced rupture of this organ.

In this study an attempt was made to induce uremia by artificial rupture of the bladder and allowing the urinary waste products to be reabsorbed through the peritoneal lining. The effect of repair of the bladder defect by surgery at the end of 24 hours on the symptomatology, course, recovery rate and the pattern of B.U.N. was studied. Acutalyn R/ was administered to those animals in whom uremia was experimentally induced and to those who had the bladder defect repaired and the results tabulated.

The method of B.U.N. estimation followed in this study was the one recommended by Karr, utilizing the Klett-Summerson Photoelectric Colorimeter. It was found that the B.U.N. ranged from 10.00 mgm percent to 18.50 mgm percent with an overall average of 13.15 mgm percent in 27 apparently healthy dogs during hospitalization. This was in close agreement with the observations made by other workers.

The technique used for establishing the bladder defect in these experimental animals was essentially the same as the one followed in performing cystotomy. Following surgery an acute rapidly fatal uremia was induced in normal healthy dogs. The onset of uremia was evidenced by symptoms of polydipsia, nausea and vomition as early as the 18th hour following surgery. The patients became rapidly dehydrated and as the disease progressed became somnolent and gradually lapsed into coma, with death occurring in all the cases at varying intervals between 36 and 72 hours after surgery. The rapid

rise in the B.U.N. noticed in experimental dogs numbers 3, 4 and 6 between 24 and 48 hours was significant and might be of prognostic importance in the naturally occurring cases of rupture of this organ. After 36 hours such animals would definitely be poor surgical risks. The highest level of B.U.N. found was 293.89 mgm percent. From the observations made on the symptomatology and the pattern of B.U.N. in these dogs, it might be concluded that a B.U.N. over 40.00 mgm percent was of diagnostic importance in acute uremia.

Repair of the bladder defect at the end of 24 hours before the symptoms of uremia were well established, brought about a rapid decrease in the level of B.U.N. from the average peak of 35.53 mgm percent to an average of 18.95 mgm percent within 12 hours. During the following 36 hours recovery was apparently complete in all five of the animals in this group. The results of this experiment adequately demonstrated the prognostic significance of B.U.N. in uremia. It was apparent that the alarming symptoms of uremia developed simultaneously with the rapid increase in the B.U.N. and that the repair of the damage to the bladder wall brought about an ameliorating effect on the symptoms shown by the patient with the concomitant drop in the level of B.U.N. Following accidental rupture of the bladder the determination of the B.U.N. would be a definite aid in assessing the condition of the patient for surgery.

In the third and fourth series of experiments the effect of Acutalyn R/ on experimentally produced uremia was studied.

In the third series, Acutalyn R/ effectively controlled the level of the B.U.N. during the initial 24 hours of the disease in 6 of 8 dogs and although it delayed the onset of uremia it did not halt the fatal culmination of the disease in these animals. In fact after the initial 24 hours following

surgery, the B.U.N. rose at a rapid rate and all the animals succumbed to the disease in the course of 48 to 84 hours.

The fourth series of experiments demonstrated the combined effect of Acutalyn R/ and the surgical repair of the bladder defect. All the animals in this group made an uneventful recovery under the protective influence of this drug. The B.U.N. dropped to within normal range within 24 hours following surgical repair. Early surgical repair alone did bring about a satisfactory cure of the condition as demonstrated in the second series of experiments. However the shorter crest in the percentage increase of B.U.N. shown in Fig. 9 compared to the one shown in case of repair (in the same figure), correlated with the clinical observations would definitely establish the efficacy of Acutalyn R/ in suppressing the B.U.N. The value of Acutalyn R/ is thought to lie in its ability to aid in controlling the early shock due to surgery and perhaps in counteracting the biochemical changes in the tissues to bring about a dramatic recovery from acute uremia.